

# Large Scale Biomarker Discovery and Validation for Parkinson Disease

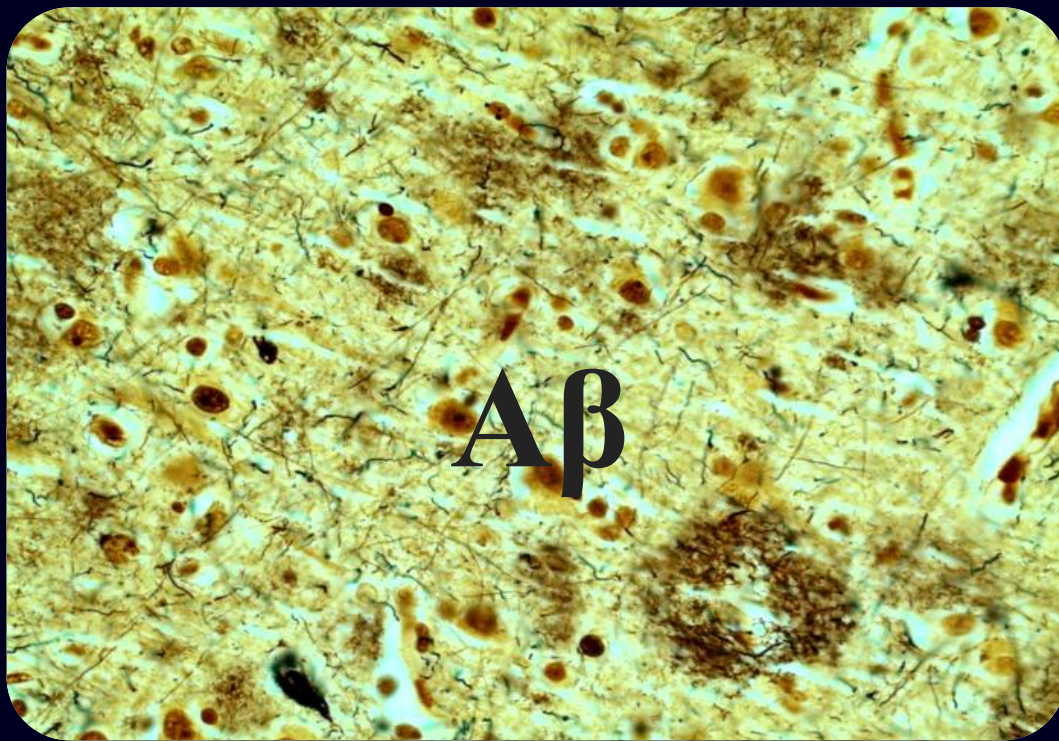
**PDBP Launch Meeting, Arlington, VA  
November 13-14, 2012**

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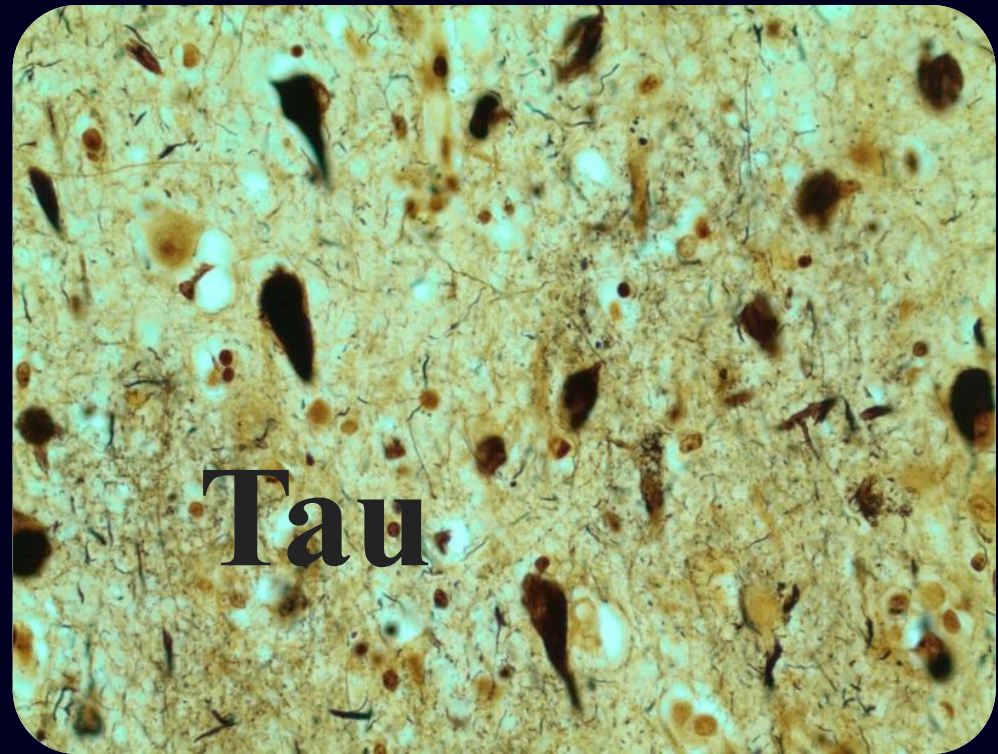
Departments of Neurology, Ophthalmology and Pathology  
University of Washington School of Medicine



# Alzheimer Disease



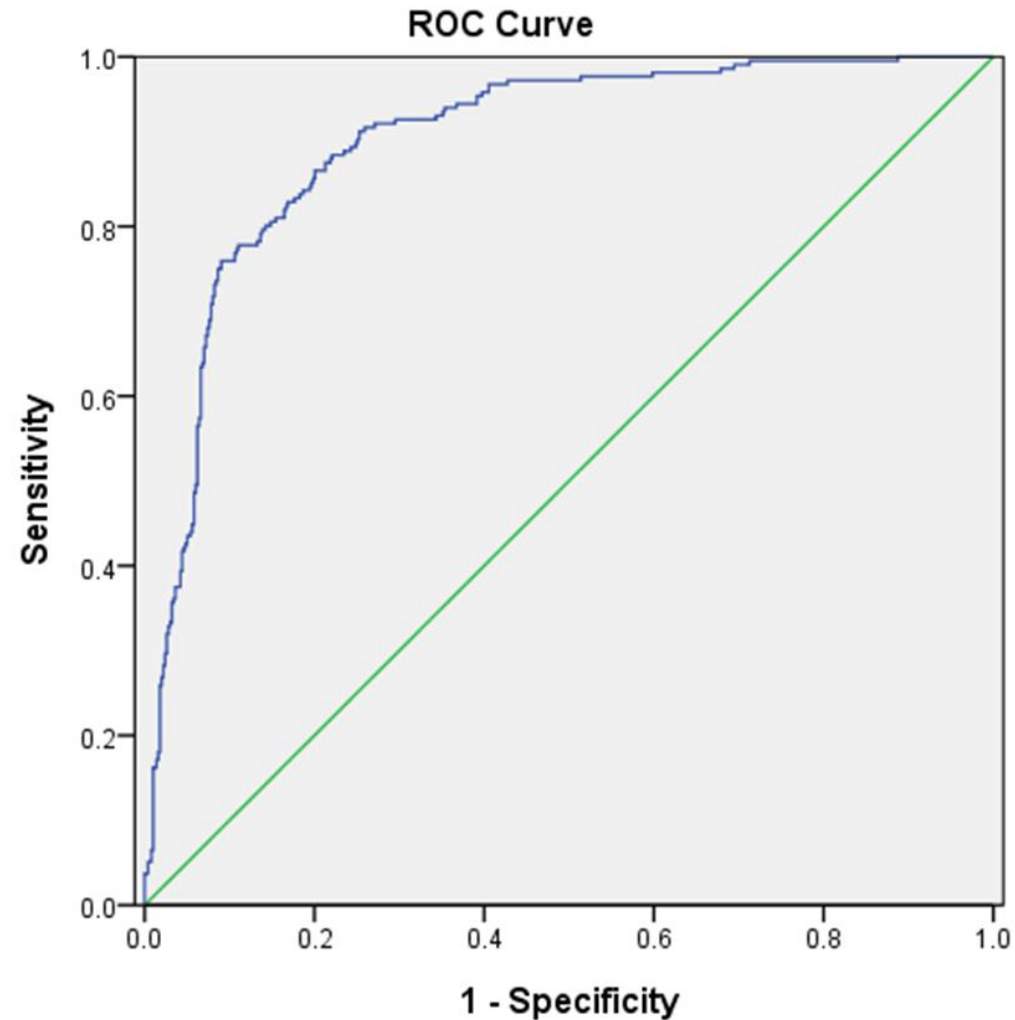
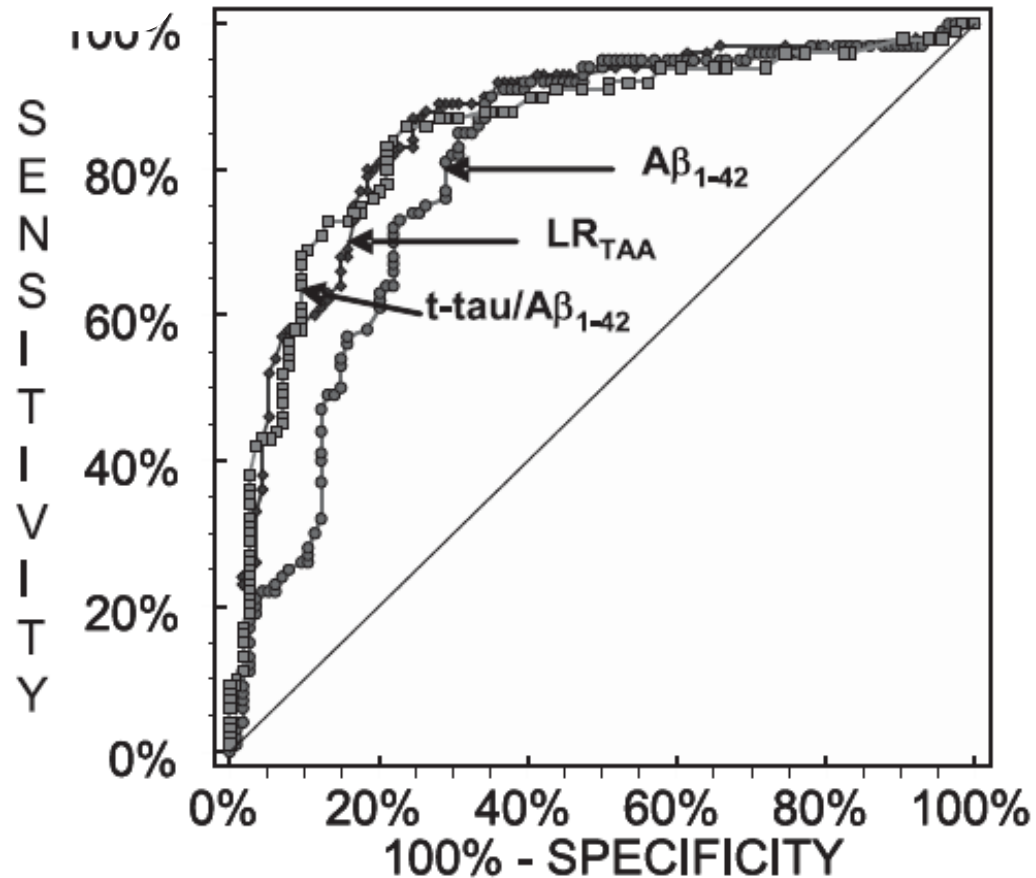
**Plaques**



**Tangles**

# ROC Analysis Based on CSF A $\beta$ and Tau

ADNI BASELINE CSF

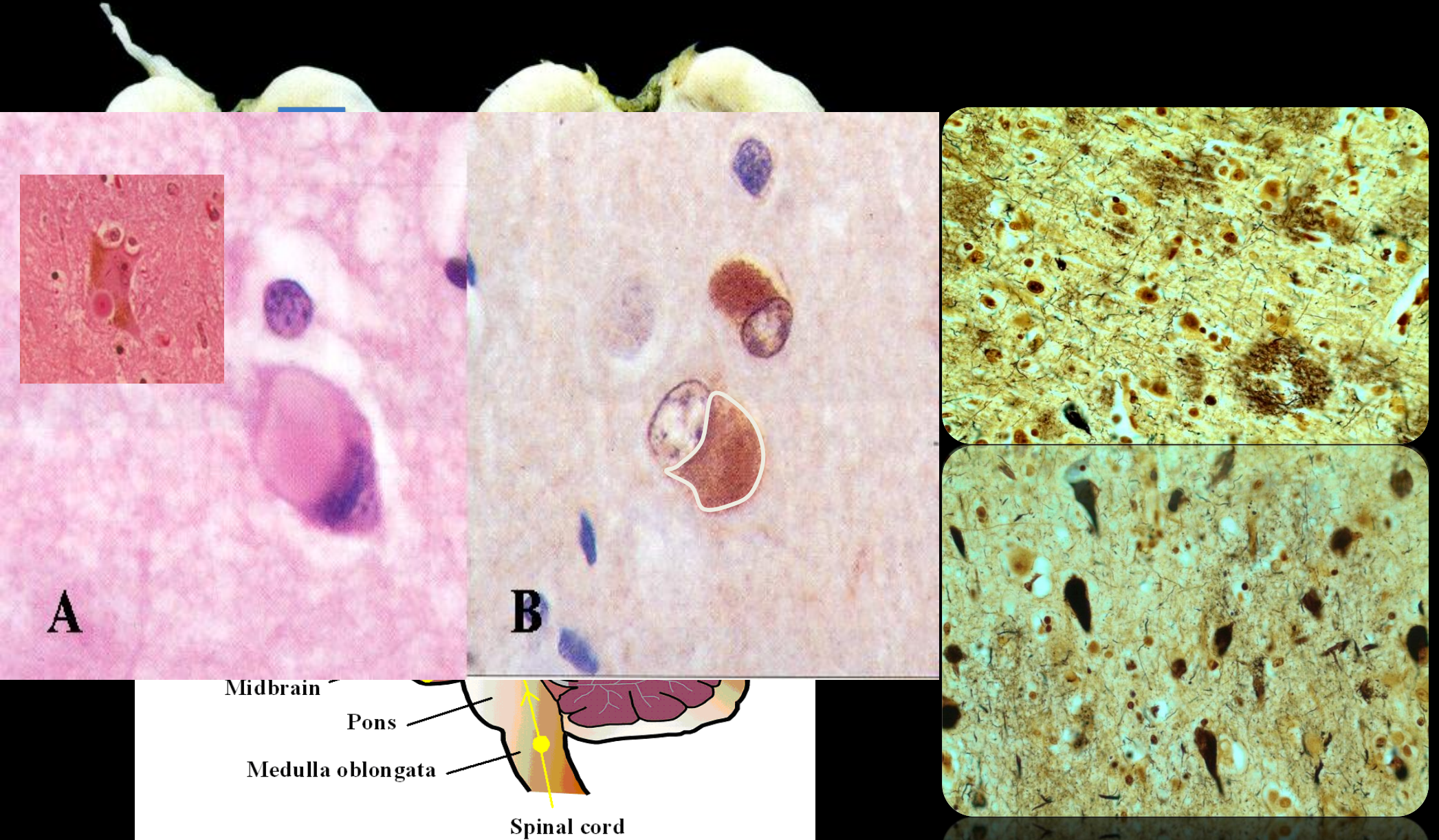


Annals of Neurology, 2009

UW



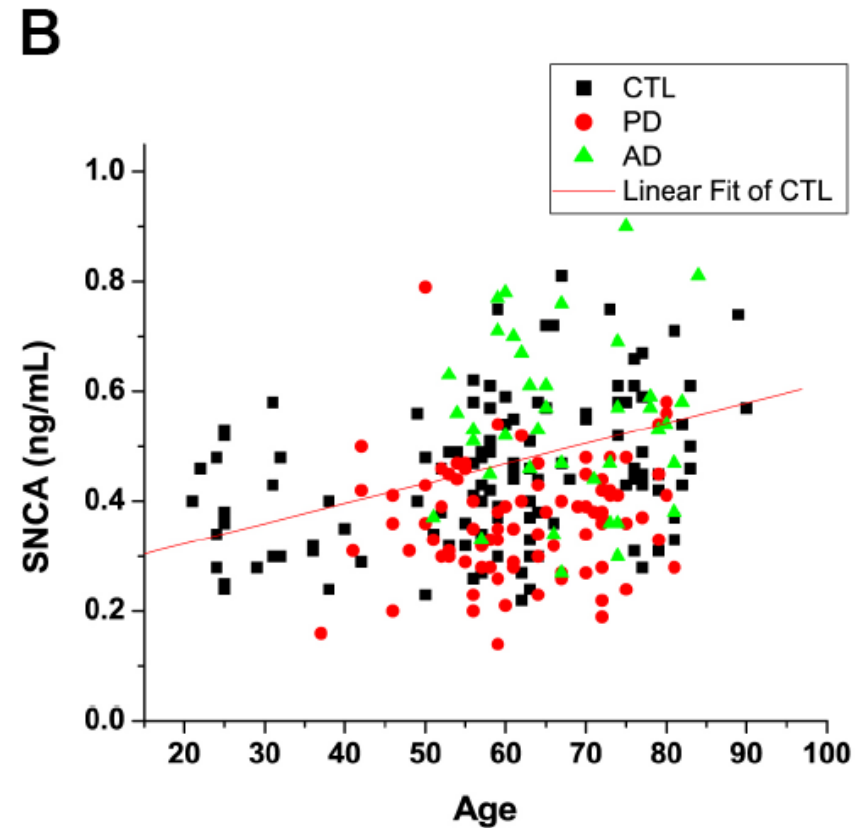
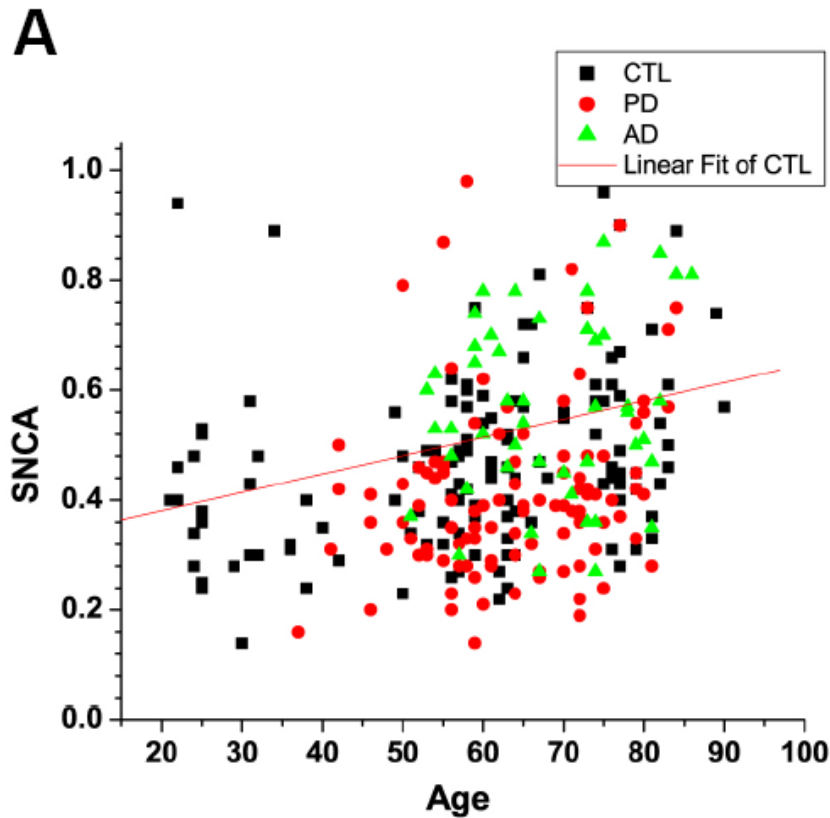
# Parkinson Disease





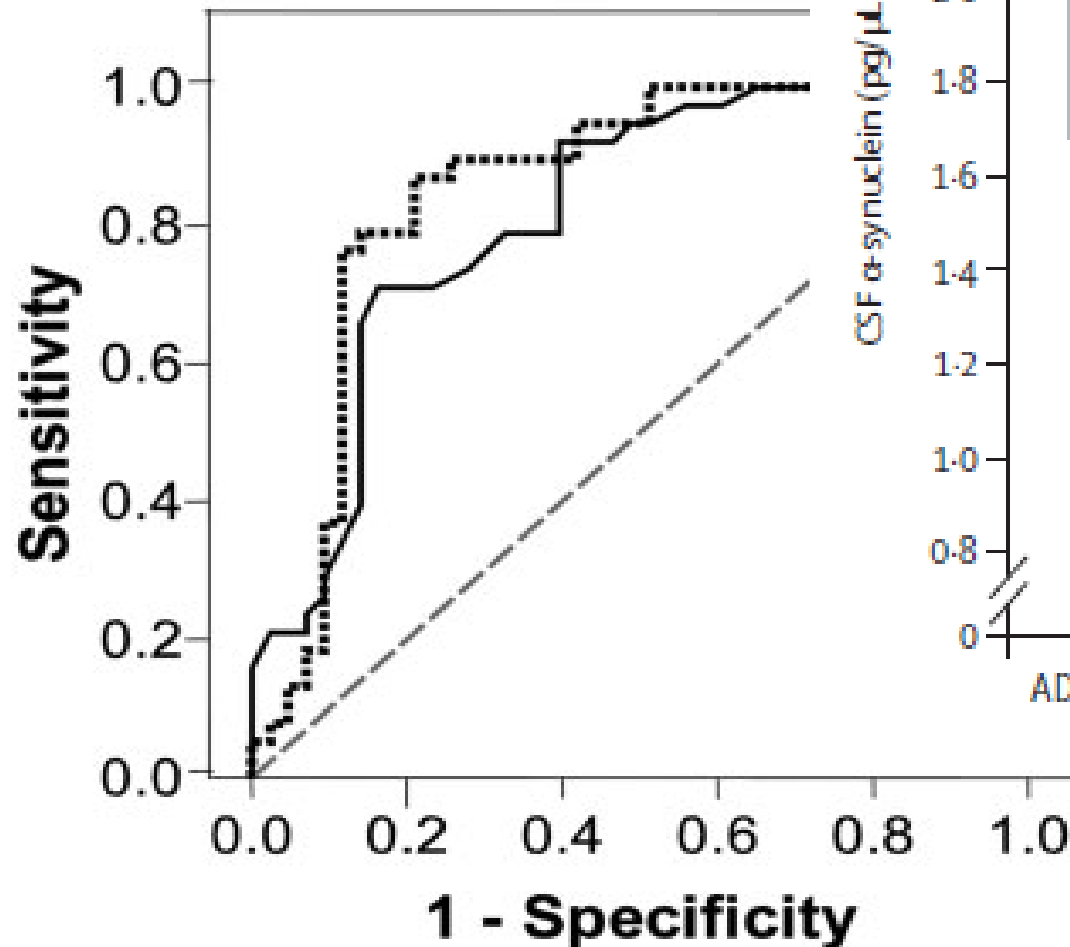
# $\alpha$ -Syn in PD and AD

## Brain, 2010



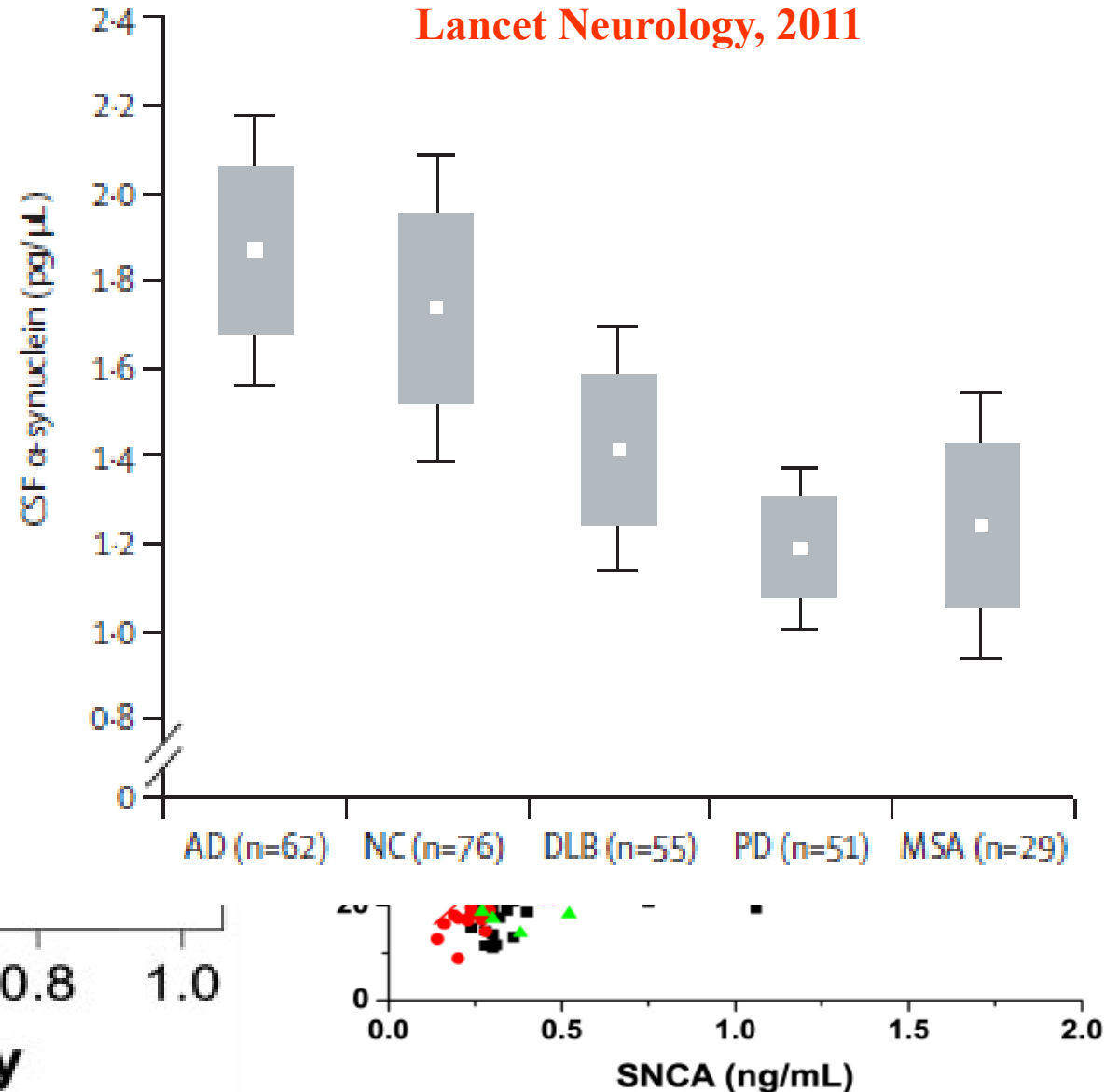
# Diagnostic value of $\alpha$ -Syn and DJ-1

Brain, 2010

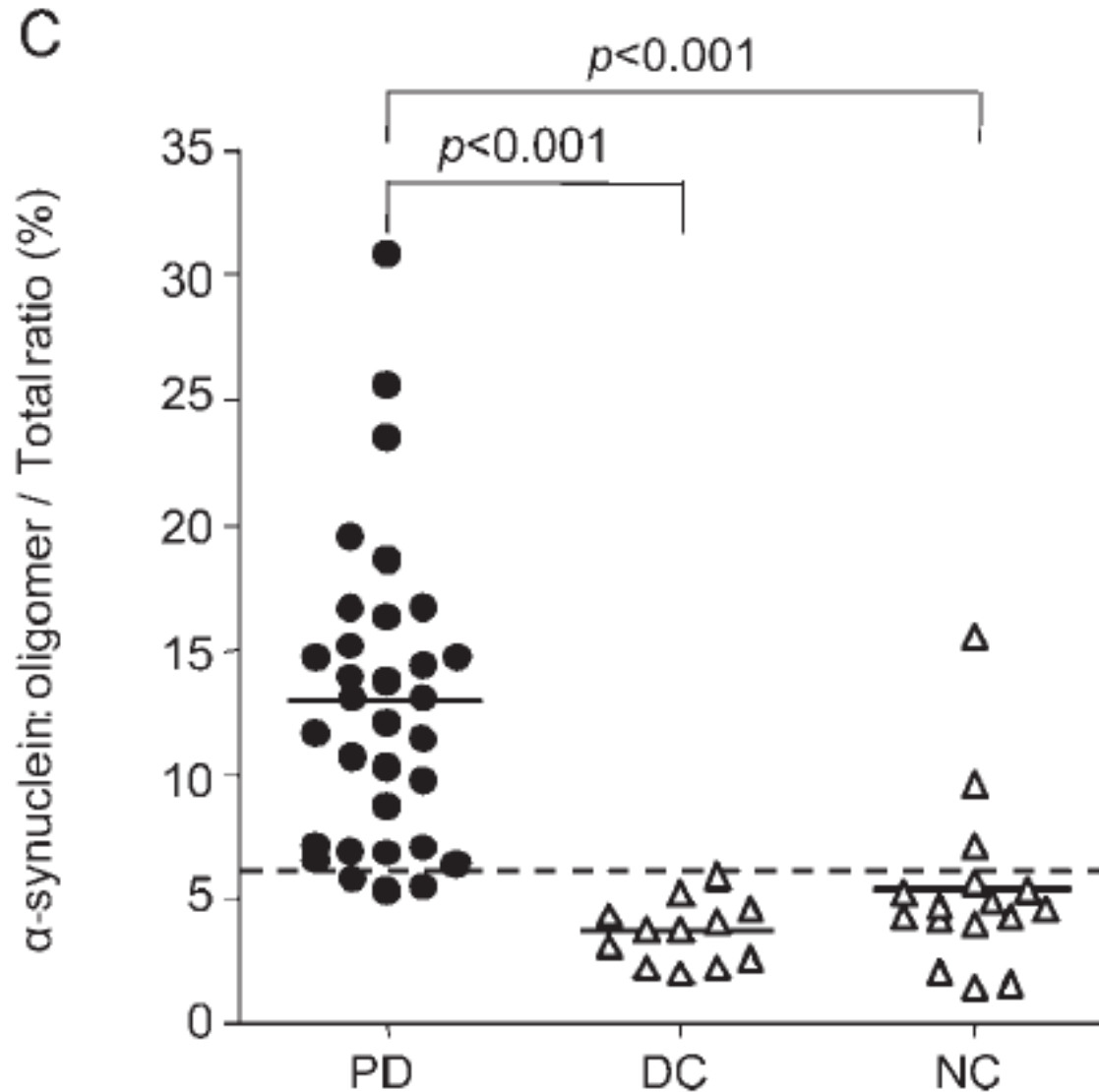


A

Lancet Neurology, 2011

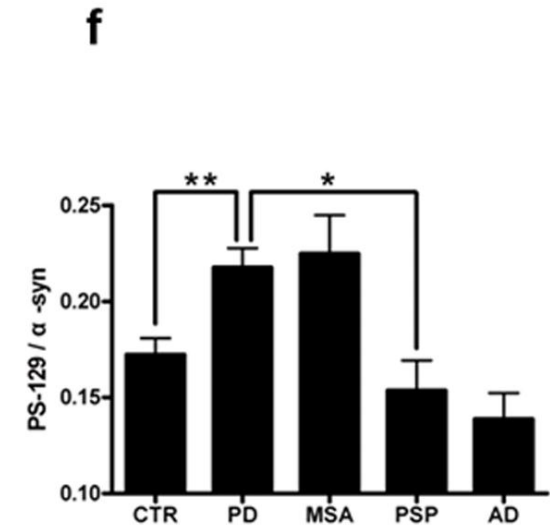
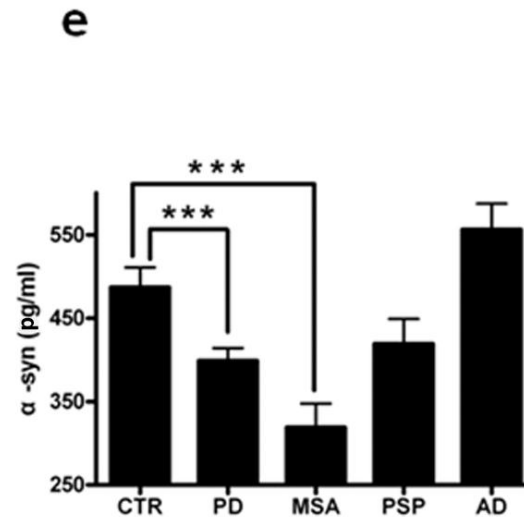
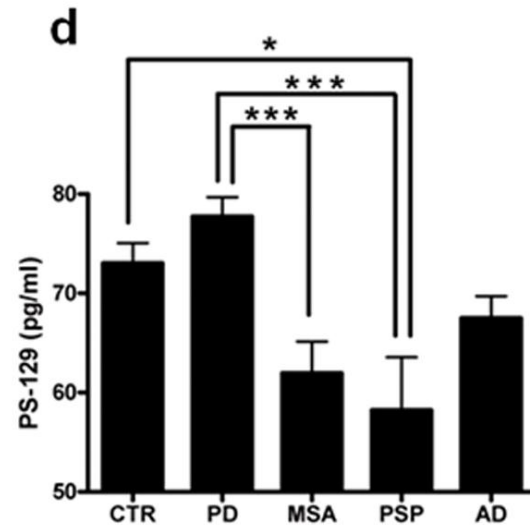
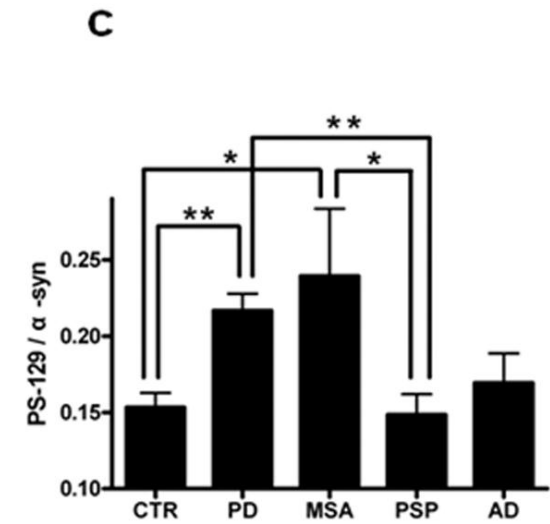
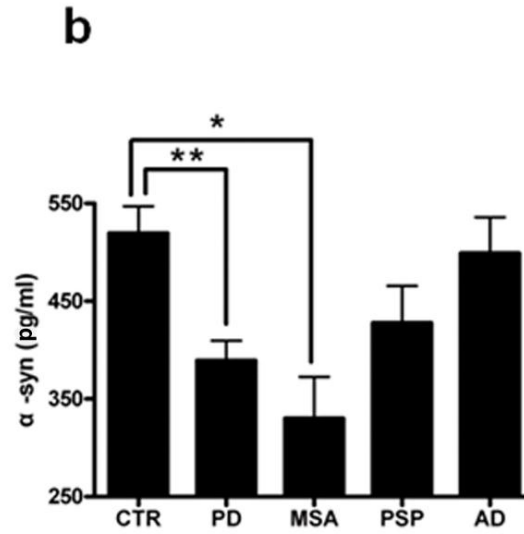
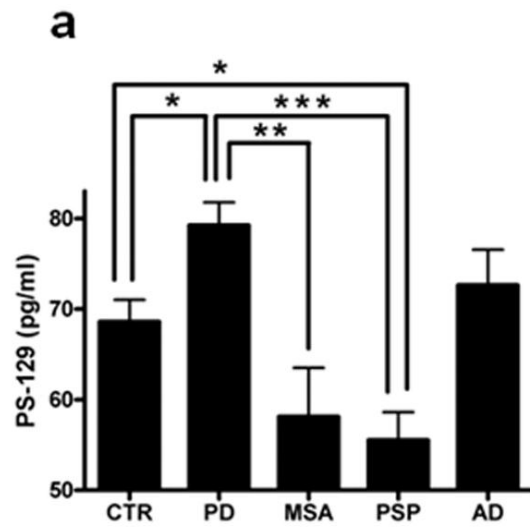


# Oligomeric $\alpha$ -Syn - Neurology 2012



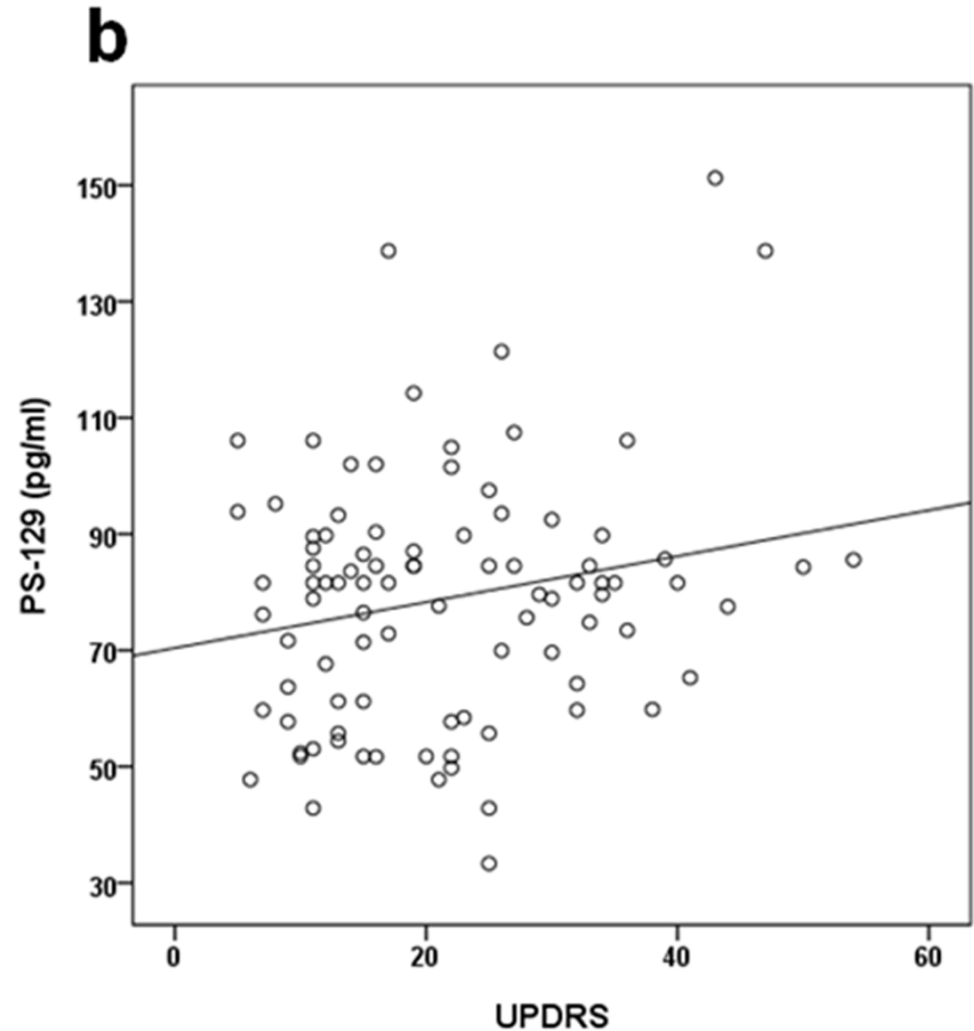
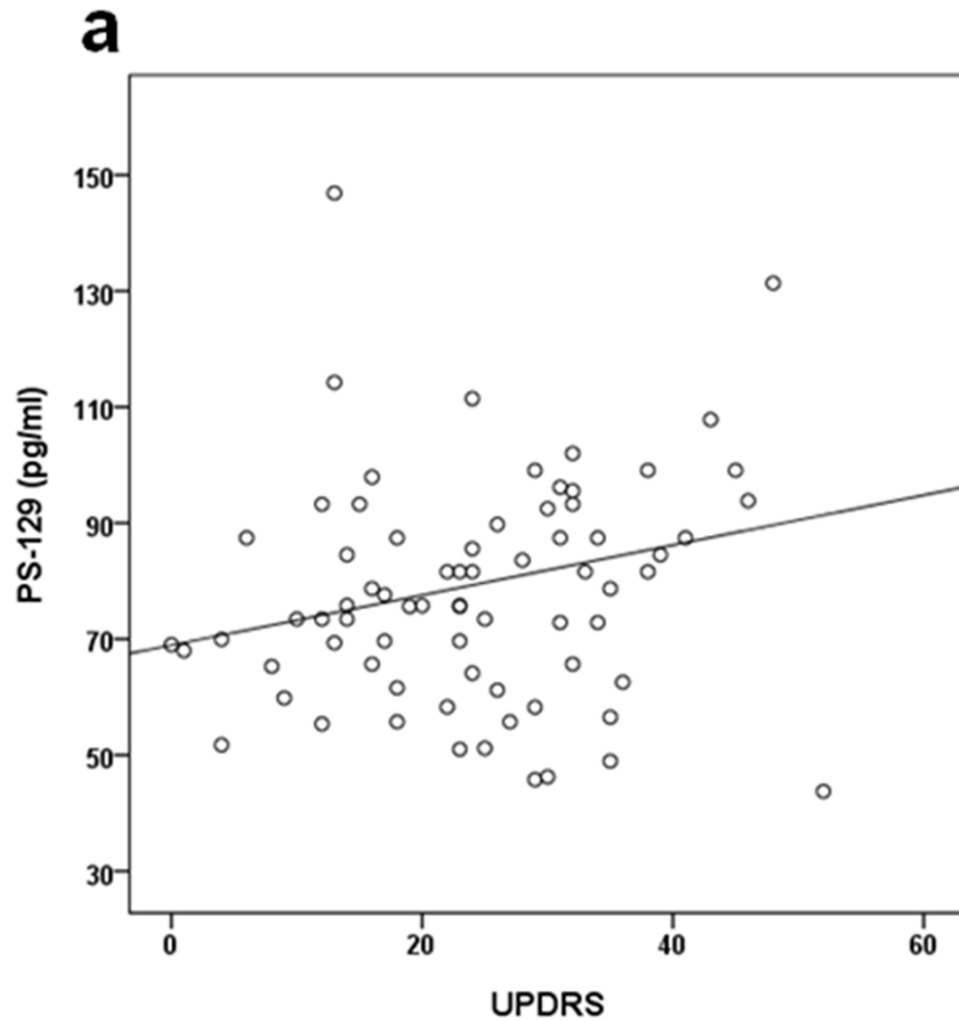


# PS129 in PD - Science (Transl Med), 2012





# PS129 in PD - Science (Transl Med), 2012;4:121

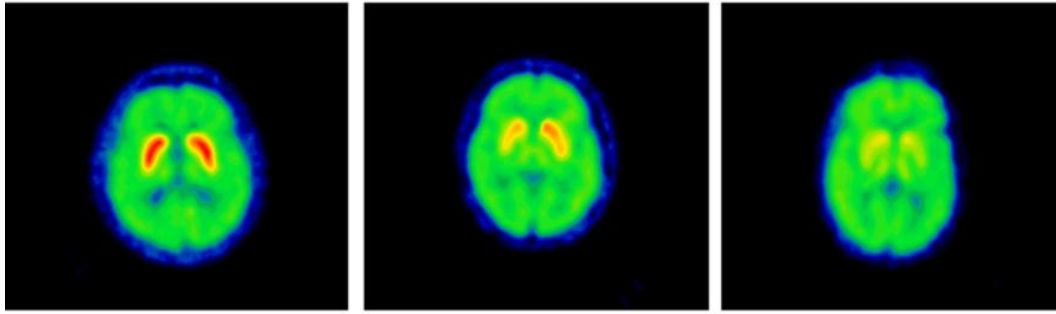


# CSF Tau, P-tau and A $\beta$ in PD

**Annals of Neurol, 2011**

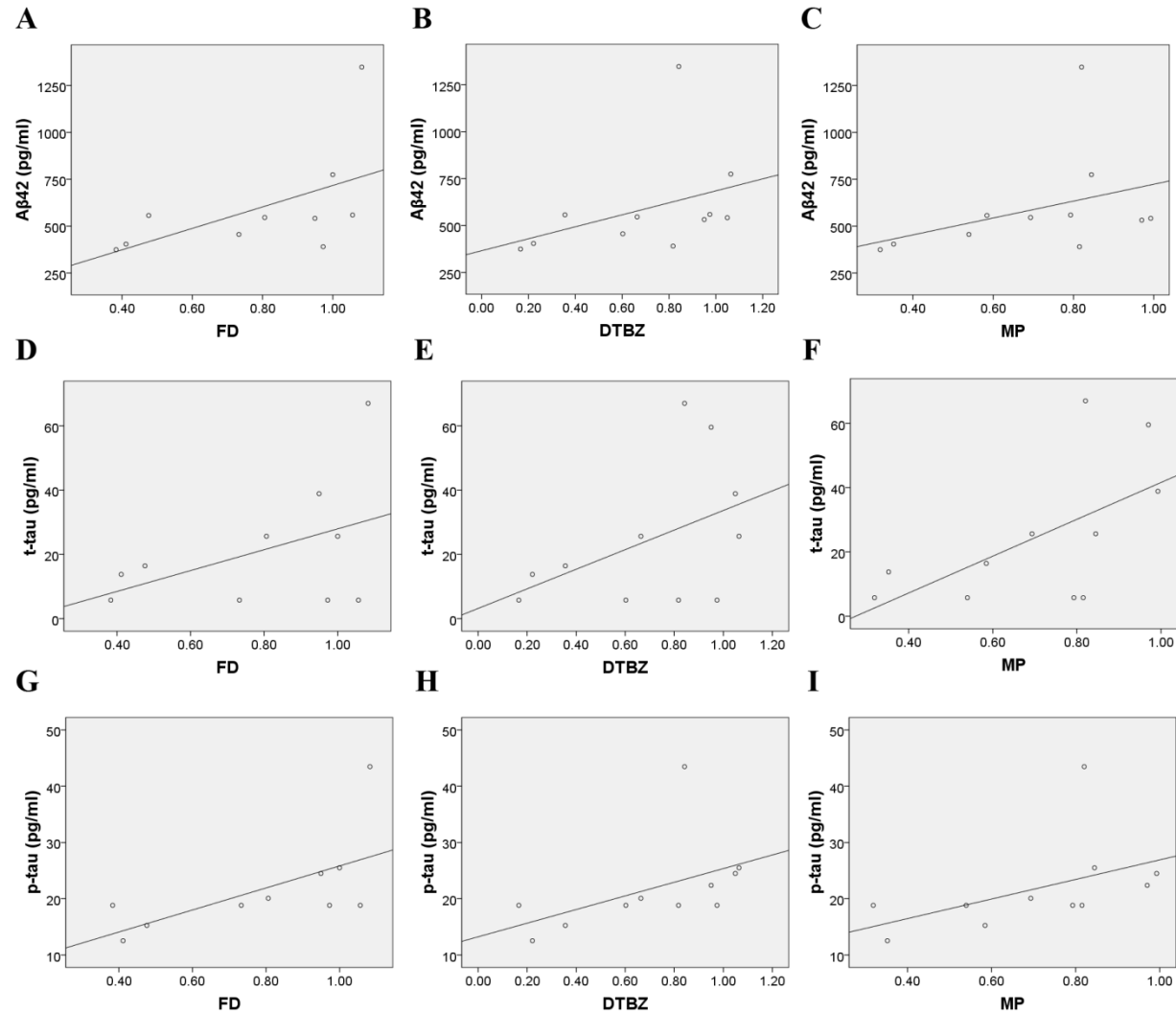
	Crossectional (Baylor, OHSU and UW)			Crossectional (NIH + Norway)		
	CTRL (n=126)	PD (n=135)	<i>P</i> Values	CTRL (n=74)	PD (n=46)	<i>P</i> Values
A $\beta$ (pg/ml)	410.5 $\pm$ 174.4	331 $\pm$ 126 ↓	.026	557.7 $\pm$ 121.5	376.1 $\pm$ 121.5 ↓	.000
P-tau (pg/ml)	28.1 $\pm$ 16.5	21 $\pm$ 7.6 ↓	<.001	48.3 $\pm$ 21.1	30.6 $\pm$ 11.5 ↓	.001
Tau (pg/ml)	62.7 $\pm$ 19.8	54.1 $\pm$ 15.1 ↓	.003	60.9 $\pm$ 23.1	43.7 $\pm$ 12.5 ↓	.021

A control asymptomatic PD

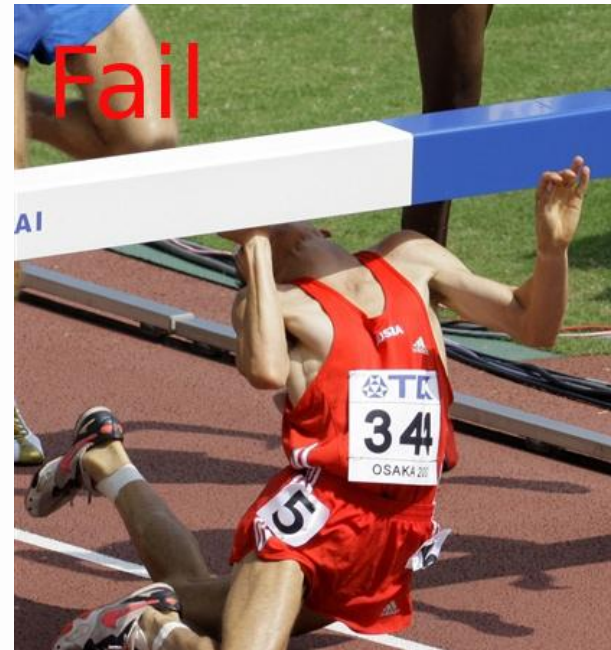


# *LRRK2* Patients

Neurology. 2012;78:55-61



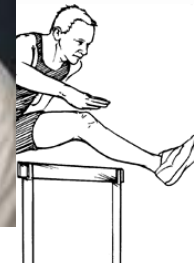
# Roadmap and Strategies to Success





# Cohorts and Sample Collection

## Udall, ADRC and others



PANUC  
*Pacific Northwest Udall Center*





**Promising Candidates**



# Results of Proteomic Profiling

## Brain: >4,000 proteins identified

Midbrain and cortical proteome

Total, glycoproteins, phosphoproteins , oxidized and ubiquitinated proteins

Isoforms of key proteins by 2D gel

## CSF: >3,000 proteins identified

Total unbiased profiling

Glycoproteins and inflammatory mediators

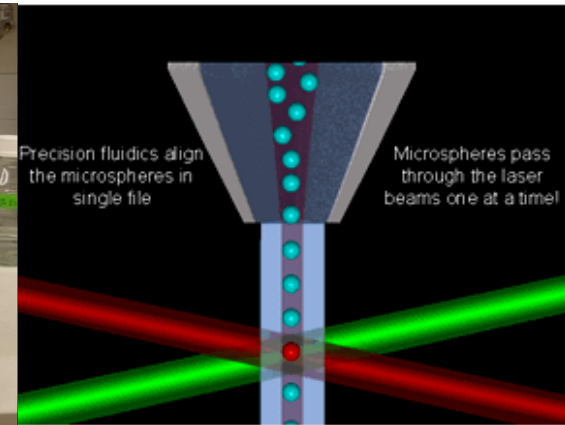
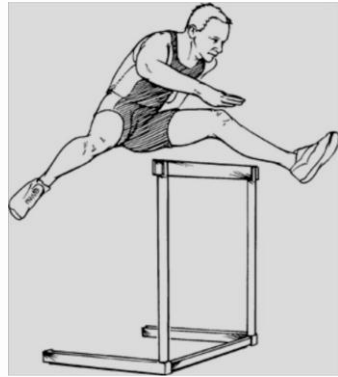
Exosomes

Isoforms of key proteins by 2D gel

## Proteins altered in abundance for validation

Promising candidate proteins (Luminex) and peptides - MRM

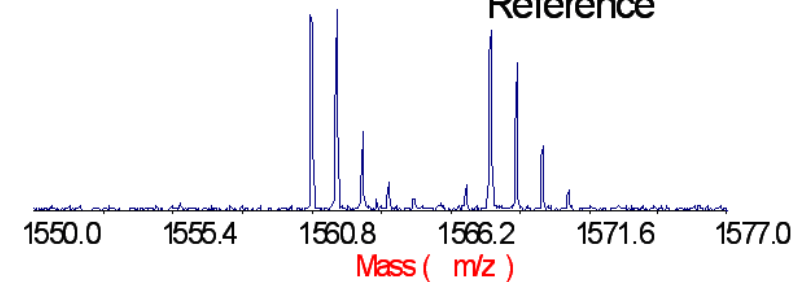
# Candidates Proteins and Peptides



AQLLQGLGFN\* L<sup>#</sup>TER  
(Corticosteroid -binding globulin)

Endogenous

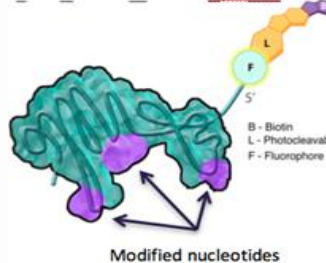
Reference







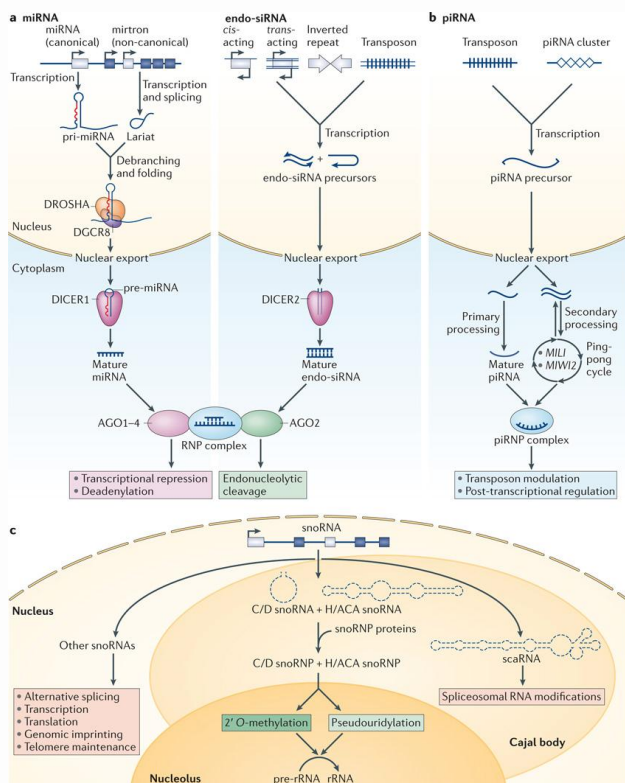
Slow Off-rate Modified Aptamer



SOMAmers have two basic properties: a unique shape to bind proteins (pink) and a measurable DNA sequence



Qureshi & Mehler



Other markers  
and platforms

Long and short ncRNAs

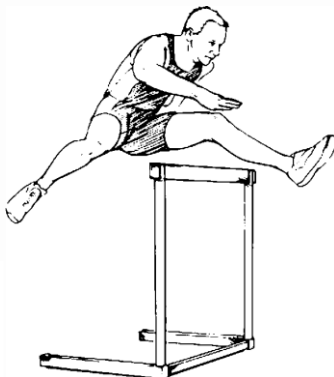
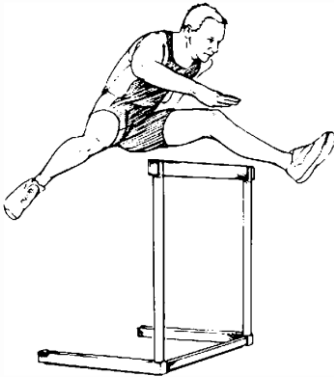
microRNAs

tRNAs and rRNAs

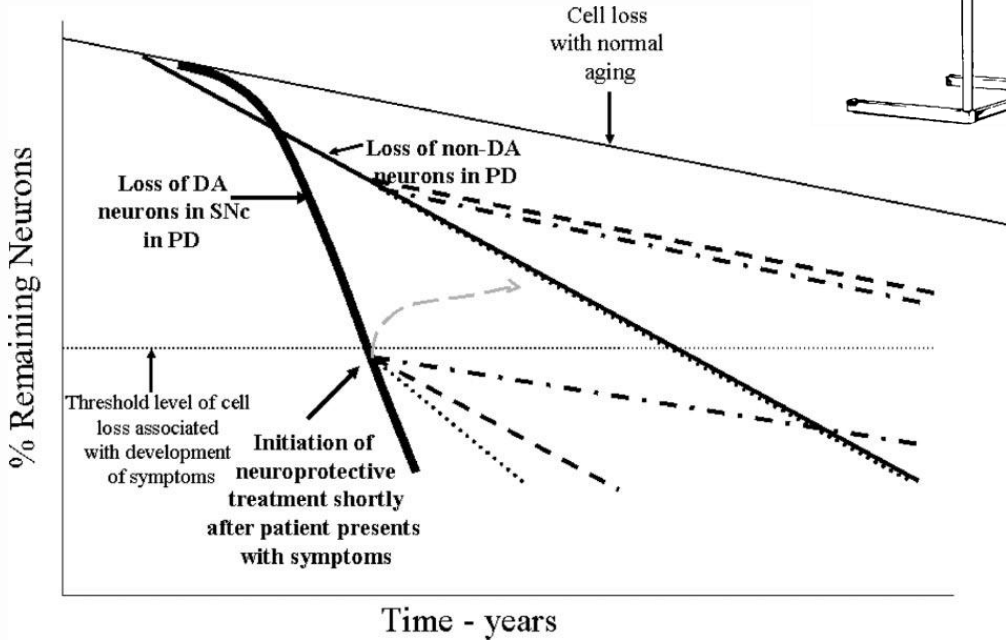
snoRNAs

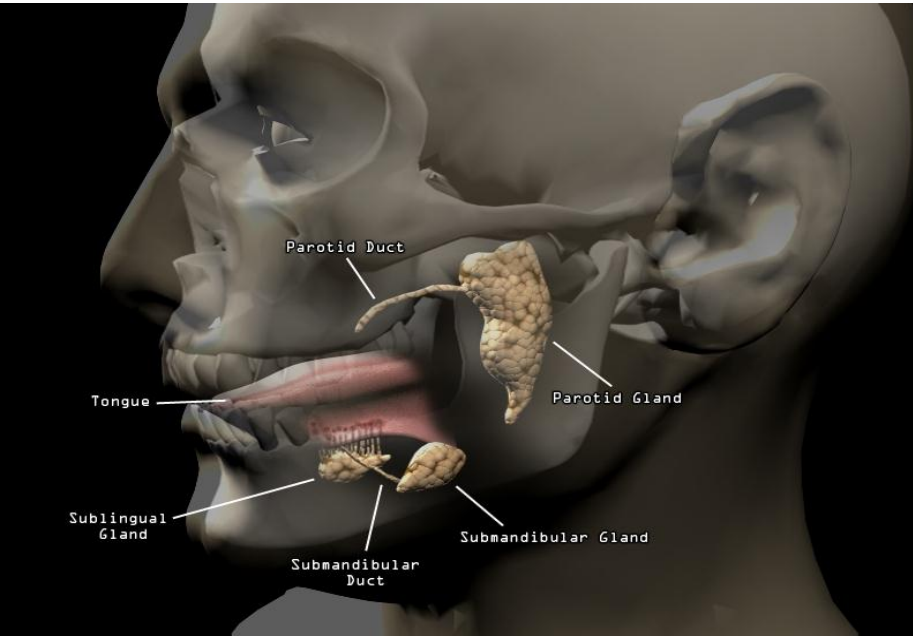
piRNAs (DICER independent)





**THE MICHAEL J. FOX FOUNDATION  
FOR PARKINSON'S RESEARCH**

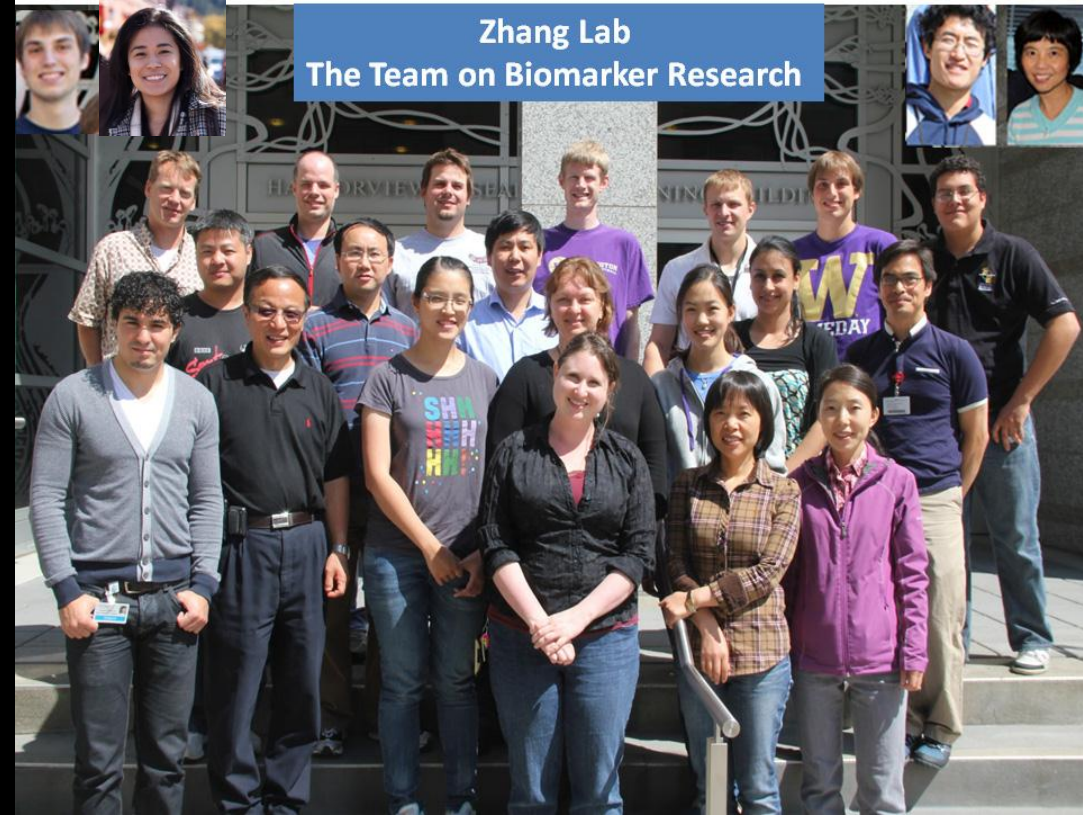






# People who did the work

\$\$\$ - NIH  
Fox, APDA and PDF



- **CSF Collection (controls, PD and other diseases):**
  - 1) Baylor (Jankovic)
  - 2) OHSU (Chung, Quinn, and Nutt)
  - 3) UCSD (Glasko)
  - 4) UWSM (Leverenz, Peskind, Samii, and Zabetian)
  - 5) NIH (Goldstein)
  - 6) U Penn (Siderowf)
- **LRRK2 Project:** CSF - JA (Norway), KH (Japan), JL and CZ (UW, USA, as well as ZW and RU (Mayo, US); PET - JS (Canada)